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     (FILE 'HOME' ENTERED AT 07:42:02 ON 28 FEB 2005)

     FILE 'CAPLUS' ENTERED AT 07:42:13 ON 28 FEB 2005
L1          1213 S (PALLADIUM(L)PLATINUM)(L)HYDROGENA?
L2             0 S L1(L)DONEPEZIL?
L3             0 S L1 AND DONEPEZ?
L4             4 S L1 AND (PYRIDIN?(L)PIPERIDIN?)
L5            11 S DONEPEZ? (L)((PALLAD? OR PD) OR (PLATIN? OR PT))
L6             3 S L5 AND PY<+2002
L7             4 S L5 AND PY<=2002

=> s l5 not l7
L8             7 L5 NOT L7

=> d bib hit 1-7

L8   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:1122813  CAPLUS
TI   Concurrent administration of donepezil HCl and levodopa/carbidopa in
     patients with Parkinson's disease: assessment of pharmacokinetic changes
     and safety following multiple oral doses
AU   Okereke, Chukwuemeka S.; Kirby, Louis; Kumar, Dinesh; Cullen, Edward I.;
     Pratt, Raymond D.; Hahne, William A.
CS   Clinical Pharmacology, Eisai Medical Research Inc., Ridgefield Park, NJ,
     USA
SO   British Journal of Clinical Pharmacology (2004), 58(Suppl. 1), 41-49
     CODEN: BCPHBM; ISSN: 0306-5251
PB   Blackwell Publishing Ltd.
DT   Journal
LA   English
RE.CNT  36    THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB   Aim The use of acetylcholinesterase inhibitors for the treatment of
     comorbid Alzheimer's disease in Parkinson's disease (PD)
     patients stabilized on a levodopa regimen may potentially disrupt
     cholinergic balance. This randomized, double-blind, crossover study
     investigated the safety of, and possible drug-drug interaction between,
     donepezil HCl and levodopa/carbidopa. Methods Twenty-five
     patients with PD who were taking physician-optimized doses of
     levodopa/carbidopa (with daytime dosing intervals of 4-8 h) were
     administered once-daily doses of either donepezil HCl (5 mg) or
     placebo for 15 days, in two treatment periods, separated by a washout of at
     least 2 wk. Some patients took a second dose of levodopa/carbidopa after
     4 h, therefore subanal. of the levodopa/carbidopa data was conducted up to
     4 h and 8 h after dosing. Twenty-six healthy matched controls received
     open-label donepezil HCl only, for a single 15-day period.
     Blood samples were collected before, during and after the 15 doses of
     donepezil HCl for pharmacokinetic (PK) assessments.
     Pharmacokinetic parameters included maximum attained plasma drug concentration
     (Cmax), time at which Cmax is attained (tmax), plasma drug concentration at
     steady state (CSS), and area under the drug concentration-time curve over the
     dosing interval. Safety assessments included monitoring adverse events,
     and the Unified Parkinson's Disease Rating Scale (UPDRS) motor examination
     Results The mean age of all subjects was 72.6 ± 1.3 years.
     Donepezil PK assessments of PD patients receiving
     levodopa/carbidopa were similar to the PK results from healthy controls
     who received donepezil HCl only (mean AUC0-12 h = 281.6 ±
     17.6 and 268.6 ± 19.9 ng·h ml-1, resp.). Carbidopa PK were not
     significantly altered by the concomitant administration of multiple doses
     of donepezil HCl, compared with when PD patients
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received placebo (mean AUC0-8 h = 921.8 ± 160 and 821.8 ± 113 ng·h ml-1, resp.). Four hours after administration of **donepezil** HCl in **PD** patients, AUC0-4 h, Cmax and CSS of levodopa were higher than when **PD** patients received placebo ($P < 0.05$). Eight hours after **donepezil** HCl, however, only Cmax and tmax were observed to change compared with when **PD** patients received placebo (mean Cmax = 2652 ± 429 and 2077 ± 276 ng ml-1, resp.; mean tmax = 1.7 ± 0.4 and 2.9 ± 0.5 h, resp.; $P \leq 0.05$). The number of **PD** patients who experienced at least one adverse event during the study (13/25) was higher when they received **donepezil** HCl than when they received placebo (5/25), but was the same as healthy subjects who received **donepezil** HCl only (13/26). There were no significant differences in change from baseline on the UPDRS motor examination parameters in **PD** patients when they took **donepezil** HCl and when they took placebo. Conclusions No clin. significant drug-drug interactions between **donepezil** HCl and levodopa/carbidopa were observed at steady state. The small changes in the pharmacokinetics of levodopa did not result in any change in motor symptoms. Co-administration of the two drugs led to a small increase in adverse events compared with administration of levodopa/carbidopa alone in **PD** patients. These adverse events, however, were consistent with **donepezil**'s cholinomimetic effect, and their incidence was comparable to that observed following the administration of **donepezil** HCl alone.

L8 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:1122809 CAPLUS
TI Steady-state pharmacokinetics, pharmacodynamics and tolerability of donepezil hydrochloride in hepatically impaired patients
AU Reyes, Josephine F.; Vargas, Ramon; Kumar, Dinesh; Cullen, Edward I.; Perdomo, Carlos A.; Pratt, Raymond O.
CS Clinical Pharmacology, Eisai Medical Research Inc., Ridgefield Park, NJ, USA
SO British Journal of Clinical Pharmacology (2004), 58(Suppl. 1), 9-17
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell Publishing Ltd.
DT Journal
LA English
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Aims To evaluate the pharmacokinetics (PK), pharmacodynamics (**PD**), tolerability and safety of **donepezil** HCl 5 mg following oral doses for 1 and 24 days in hepatically impaired patients compared with healthy controls under steady-state, multiple-dose conditions. Methods in this single-center, multiple-dose, open-label study, patients with impaired hepatic function (Child-Pugh grade A or B) and healthy controls (matched by gender, age and weight to the hepatically impaired patients) received a single 5 mg dose of **donepezil** on day 1 and then **donepezil** HCl 5 mg once daily from days 6 to 29. PK and **PD** (determination of erythrocyte acetylcholinesterase inhibition) parameters were evaluated on days 1 and 29. Treatment-emergent adverse events (AEs), vital signs, phys. examination and clin. laboratory test parameters
were monitored throughout the study. Results A total of 35 subjects (18 patients with hepatic impairment and 17 healthy controls) were enrolled and 32 subjects (16 in each group) completed the study. On day 1 (following a single dose) hepatically impaired patients showed a significant decrease in Tmax, while t1/2 and AUC0-∞ were significantly increased compared with the healthy controls. On day 29 (following multiple doses), AUC0-24 h, Cmax, t1/2, CSS, and RA were significantly increased in hepatically impaired patients compared with healthy controls. AUC0-24 h increased by 47.6% in the patients with hepatic impairment compared with the healthy controls. There were no

significant differences in **PD** between the groups, although at steady state, the mean AChE inhibition was 16.2% higher in the hepatically impaired patients. No serious AEs were reported and no subject withdrew from the study due to AEs. The most common AEs in both groups were headache and diarrhoea. No clin. significant changes from baseline were observed in vital signs, phys. examination findings or electrocardiograms. There was a significant difference in the number of hepatically impaired subjects with abnormalities in serum glucose compared with healthy subjects. However, these elevations were not associated with AEs. Conclusions The results of this study suggest that patients with AD and mild to moderate hepatic impairment (Child-Pugh grade A or B) can be safely given **donepezil** 5 mg once daily and that this dose is associated with a nonsignificantly higher AChE inhibition than age-matched volunteers.

L8 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:802718 CAPLUS
DN 141:314158
TI Process for the preparation of donepezil and derivatives thereof
IN Kumar, Yatendra; Prasad, Mohan; Nath, Asok; Maheshwari, Nitin
PA Ranbaxy Laboratories Limited, India
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004082685	A1	20040930	WO 2004-IB843	20040322

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI IN 2003-DE352 A 20030321
OS CASREACT 141:314158; MARPAT 141:314158
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 75-58-1, Tetramethylammonium iodide 311-28-4, Tetrabutylammonium iodide 497-19-8, Sodium carbonate, uses 554-13-2, Lithium carbonate 584-08-7, Potassium carbonate 1643-19-2, Tetrabutylammonium bromide 7440-05-3D, **Palladium**, on carbon 7440-06-4D, **Platinum**, on carbon 7440-16-6D, Rhodium, on carbon 7664-41-7, Ammonia, uses 11113-84-1, Ruthenium oxide 11129-89-8, **Platinum** oxide 37143-59-2 49550-01-8 180418-66-0
RL: CAT (Catalyst use); USES (Uses)
(preparation of **donepezil** and derivs.)

L8 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:652671 CAPLUS
DN 141:174080
TI Hydrogenation and benzylation process for the preparation of 1-benzyl-4-[[5,6-dimethoxy-1-indanon)-2-yl]methyl]piperidine hydrochloride (donepezil hydrochloride)
IN Radhakrishnan, Tarur Venkatasubramanian; Govind, Sathe Dhanajay; Venkatraman, Naidu Avinash
PA India

SO U.S. Pat. Appl. Publ., 5 pp., Cont.-in-part of U.S. Ser. No. 365,717.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004158070	A1	20040812	US 2003-714724	20031117
US 6649765	B1	20031118	US 2003-365717	20030212
PRAI US 2003-365717	A2	20030212		

OS CASREACT 141:174080
AB A process for the preparation of 1-benzyl-4-[[(5,6-dimethoxy-1-indanon)-2-yl]methyl]piperidine hydrochloride (i.e., **donepezil** HCl; m.p. 210-212°) is described in which 5,6-dimethoxy-2-[(pyridin-4-yl)methyl]inda-1-one is hydrogenated with a noble metal catalyst (e.g., **Pd**/C) or a non-oxide derivative of a noble metal catalyst in a solvent at 20-100°/10-90 psi-gauge to give 4-[[(5,6-dimethoxy-1-indanon)-2-yl]methyl]piperidine which is benzylated with benzyl bromide at 20-80° followed by salification with methanolic HCl.
IT Hydrogenation catalysts
(chemoselective; **Pt**-Group metals in a hydrogenation and benzylation process for the preparation of 1-benzyl-4-[[5,6-dimethoxy-1-indanon)-2-yl]methyl]piperidine hydrochloride (**donepezil** hydrochloride))
IT **Platinum**-group metals
RL: CAT (Catalyst use); USES (Uses)
(hydrogenation catalysts in a hydrogenation and benzylation process for the preparation of 1-benzyl-4-[[5,6-dimethoxy-1-indanon)-2-yl]methyl]piperidine hydrochloride (**donepezil** hydrochloride))
IT 7647-10-1, **Palladium** chloride 10049-07-7, Rhodium chloride 10049-08-8, Ruthenium chloride 10489-46-0, Rhodium sulfate 13566-03-5, **Palladium** sulfate 41860-99-5, Ruthenium sulfate
RL: CAT (Catalyst use); USES (Uses)
(hydrogenation catalyst in a hydrogenation and benzylation process for the preparation of 1-benzyl-4-[[5,6-dimethoxy-1-indanon)-2-yl]methyl]piperidine hydrochloride (**donepezil** hydrochloride))
IT 7440-05-3, **Palladium**, uses 7440-16-6, Rhodium, uses 7440-18-8, Ruthenium, uses
RL: CAT (Catalyst use); USES (Uses)
(in a hydrogenation and benzylation process for the preparation of 1-benzyl-4-[[5,6-dimethoxy-1-indanon)-2-yl]methyl]piperidine hydrochloride (**donepezil** hydrochloride))

L8 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:589284 CAPLUS
DN 141:123572
TI Process for preparation of donepezil
IN Reddy, Manne Satyanarayana; Eswaraiah, Sajja; Thippannachar, Mathad Vijayavitthal; Chandrashekar, Elati Ravi Rama; Kumar, Podichetty Anil; Kumar, Kolla Naveen
PA Reddy's Laboratories Limited, India; Reddy's Laboratories, Inc.
SO U.S. Pat. Appl. Publ., 7 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004143121	A1	20040722	US 2003-626499	20030724
PRAI IN 2002-MA555	A	20020724		

OS CASREACT 141:123572
AB An efficient process for preparation of **donepezil** I is provided. In one embodiment, the process for preparation of **donepezil** includes

suspending a catalyst, which is **palladium** metal on carbon and the compound II in an alc. solvent and hydrogenating the suspension at the hydrogen pressure of from about 1 to about 5 and a temperature of from about 40 to about 90°C till the hydrogenation reaction is substantially complete to obtain a compound III which then is converted to **donepezil** by alkylation with benzyl bromide. The processes of the invention are believed to be simple, eco-friendly, and com. viable.

IT 7440-05-3, **Palladium**, uses
RL: CAT (Catalyst use); USES (Uses)
(process for preparation of **donepezil** by hydrogenation of 5,6-dimethoxy-2-[(pyridin-4-yl)methylene]indan-1-one and subsequent alkylation with benzyl bromide)

L8 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:95406 CAPLUS
DN 140:146012
TI Process for the preparation of donepezil
IN Kaspi, Joseph; Lerman, Ori; Arad, Oded; Alnabari, Mohammed; Sery, Yana
PA Chemagis Ltd., Israel
SO Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1386607	A1	20040204	EP 2003-253336	20030528
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CA 2429563	AA	20040130	CA 2003-2429563	20030523
JP 2004131465	A2	20040430	JP 2003-154618	20030530
US 2004048893	A1	20040311	US 2003-459662	20030611
US 6844440	B2	20050118		
PRAI IL 2002-150982	A	20020730		

OS CASREACT 140:146012; MARPAT 140:146012
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 7440-05-3, **Palladium**, uses 7440-06-4, **Platinum**, uses
10035-10-6, Hydrogen bromide, uses
RL: CAT (Catalyst use); USES (Uses)
(preparation of **donepezil**)

L8 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:903267 CAPLUS
DN 139:381380
TI Process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride (donepezil hydrochloride)
IN Vidyadhar, Joshi Shreerang; Venkatraman, Naidu Avinash; Pandurang, Sutar Rajiv
PA USV Limited, BSD Marg., India
SO U.S., 3 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6649765	B1	20031118	US 2003-365717	20030212
US 2004158070	A1	20040812	US 2003-714724	20031117
PRAI US 2003-365717	A2	20030212		

OS CASREACT 139:381380
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride (**donepezil** HCl) is described in which 5,6-dimethoxy-2-(pyridin-4-yl)methyleneinda-1-one is hydrogenated with a **Platinum**-Group metal oxide catalyst in an organic solvent at 20-50°/10-45 psi-gauge, and the resulting 4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine is benzylated with an benzyl bromide in an organic solvent at 30-80° and salified with methanolic HCl.

IT Hydrogenation catalysts
(**Pt**-Group metal oxides in a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride (**donepezil** hydrochloride))

IT **Platinum**-group metal compounds
RL: CAT (Catalyst use); USES (Uses)
(oxides; hydrogenation catalysts in a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride (**donepezil** hydrochloride))

IT Group VIII element oxides
RL: CAT (Catalyst use); USES (Uses)
(**platinum**-group; hydrogenation catalysts in a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride (**donepezil** hydrochloride))

IT 1314-15-4, **Platinum** dioxide
RL: CAT (Catalyst use); USES (Uses)
(hydrogenation catalyst in a process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride (**donepezil** hydrochloride))